HYPERGLYCEMIA AND PERIVENTRICULAR - INTRAVENTRICULAR HEMORRHAGE IN THE PRETERM INFANT

by

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SUPERVISORY COMMITTEE APPROVAL

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ABSTRACT

Periventricular-intraventricular hemorrhage (PV-IVH) is a serious form of neonatal intracranial hemorrhage. This research was undertaken to determine the relationship between PV-IVH and hyperglycemia.

Medical records of 57 preterm infants from the University of Utah Medical Center were examined. Data collected demonstrated a significant relationship between the occurrence of a PV-IVH and a hyperglycemia episode. The severity of hyperglycemia could not predict the development of hydrocephalus.

It was concluded that the clinical value of glucose determinations may serve to identify a PV-IVH. Further research is indicated to validate these findings and to define the specifics of the relationship between these variables.

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CHAPTER I

INTRODUCTION

Periventricular-intraventricular hemorrhage (PV-IVH) is a common and serious form of neonatal intracranial hemorrhage for which there is no definite method of prevention or treatment (Cooke, 1981; de Courten & Rabinowicz, 1981; Fujimura, Salisbury, Robinson, Howatt, Emerson, Keeling & Tizard, 1979; Hambleton & Wigglesworth, 1976; Lazzara, Ahmann, Dykes, Brann & Schwartz, 1980; Wigglesworth & Pape, 1980). The development of perinatal - neonatal regionalization (Brown, 1980; Green, 1980) has resulted in dramatic improvement in survival rates of small premature infants. Because periventricular-intraventricular hemorrhage (PV-IVH) is a characteristic complication of preterm infants less than or equal to 32 weeks gestation (Cooke, 1981; de Courten & Rabinowicz, 1981; Hambleton & Wigglesworth, 1976; Towbin, 1968; Volpe, 1981; Wigglesworth & Pape, 1980), its incidence has increased with the increasing survival rate of this gestational age group. In the past 20 years, infant

mortality resulting from hyaline membrane disease has markedly decreased (Krauss, 1980), whereas the death rate for periventricular-intraventricular hemorrhage (PV-IVH) has remained almost constant (Anderson, 1977; Robinson & Desai, 1981).

PV-IVH is characterized by hemorrhage into the region of the terminal vein of the subependymal germinal matrix. The hemorrhage can remain isolated or rupture through the ependyma and into the ventricular system (Papile, Burstein, J., Burstein, R., & Koffler, 1978; Volpe, 1981; Wigglesworth & Pape, 1980). The reported incidence of hemorrhages affecting the subependymal region, with or without spread into the ventricles, are between 35 and 50% (Ahmann, Lazzara, Dykes, Brann & Schwartz, 1980; Leech & Kohnen, 1974; Levene, Fawer, and Lamont, 1982; Papile et al., 1978; Shinnar, Molteni, Gammon, D'Souza, Altman & Freeman, 1982). The mortality rate from PV-IVH ranges between 17 to 55% (Ahmann et al., 1980; Papile et al., 1978; Shinnar et al., 1982), with the overall incidence of fatal PV-IVH reported as being between one and two point five per one thousand live births (Anderson, 1977; Schoenberg, Mellinger & Schoenberg, 1977). The significance of posthemorrhagic hydrocephalus and longterm neurologic sequelae are currently under

study (Papile et al., 1978; Shinnar et al., 1982). The reported morbidity from these entities, thus far, range from 2 to 29% (Ahmann et al., 1980; Robinson & Desai, 1981; Shinnar et al., 1982).

Although this neurologic complication can be associated with a number of features, (e.g., an unexplained fall in hematocrit and/or its failure to rise following a blood transfusion, an increase in the tenseness of the anterior fontanel, and changes in the cardiorespiratory status) PV-IVH is not always clinically apparent (Fujimura et al., 1979; Lazzara et al., 1980; Volpe, 1981). Investigation for a more sensitive and objective clinical sign of impending PV-IVH would facilitate the identification of the onset of hemorrhage. Pinpointing the time of occurrence may result in clinical interventions which may decrease the incidence or severity of PV-IVH.

This investigator has noted that an apparent rise in serum glucose concentration as determined by Dextrostix® (Moss, 1968), precipitates the onset of the clinical signs of PV-IVH. This is the basic premise for this study.

Problem

The problem of the study was to identify if a relationship exists between the development of hyper-

glycemia and the occurrence of PV-IVH in the preterm infant.

Purpose

The purpose of this study was to determine the relationship between the onset of PV-IVH and the occurrence of hyperglycemia. If a relationship can be demonstrated, future research may be indicated to identify the specific care that could decrease the severity of PV-IVH. Ultimately, it is hoped that this endeavor will uncover clinical information which will facilitate a more rapid identification of a PV-IVH. The identification of a clinical tool to improve the observational and bedside care of infants at risk for a PV-IVH would be a significant contribution to the field of nursing.

Conceptual Framework

Abbey (1978) described a general systems theory on which this study's conceptual framework is based. She introduced the concept that all systems are organized units composed of mutually-reacting components and interacting forces. In response to various stresses and strains imposed upon the system, feedback circuits guide an internal reorganization in order to maintain an intact system. There are two

types of systems: closed and open. The closed system consists of variables that react with a predictable outcome. In contrast, the open system consists of variables that react in a continuous, orderly fashion, where the outcome is unpredictable due to the infinite number of variables.

The system, as a whole, experiences disorganization and a loss of energy, in response to a dysfunction of a part. Only the replacement of this lost energy will insure survival of the system whether open or closed (Abbey, 1978).

Man entering into an exchange with his environment is an example of an open system. The human body is an example of a closed system. The mutually reacting components of man are the various subsystems such as the glucose homeostatic mechanism. The components of this subsystem are the cells. The hormones and enzymes make up the feedback circuits which guide the system to glucose homeostasis. Components used to regulate serum glucose concentration are glucose supply, glucose utilization, and hepatic function. A change in any one of these components predictably affects blood glucose levels. Energy lost in the process of glucose homeostasis must be replaced by providing nutrients for energy in order for the system to survive.

When a system disturbance occurs, the general systems theory recognized nursing as having the potential "to facilitate energy transfer...that is needed by a system to preserve its self" (Abbey, 1978, p. 23). However, the nurse must first be able to recognize the stress and the potential strain the disturbance will cause before transferring energy back to the system, in order to preserve a homeostatic self. In this study, the research hoped to demonstrate that a disturbance, hyperglycemia, caused by a preceding stressful event (i.e., hypothermia, pneumothoraces, or even a PV-IVH), might serve as a sign of a recent or even an impending PV-IVH. Frequent measurement of glucose levels during the time of greatest occurrence of PV-IVH may give health care providers the opportunity to pinpoint the occurrence or give warning to a new or impending PV-IVH. Once alerted, initiation of therapy based on further diagnostic examination might be facilitated.

CHAPTER II

REVIEW OF LITERATURE

Glucose Homeostasis

Glucose is the primary fuel source of the neonate. It sustains the energy required for cellular metabolism. Specific organs and tissues have varying ability to utilize other substrates for energy during periods of fasting. Peripheral tissues such as muscle and fat can effectively curtail their glucose utilization (Cowett, Oh, Pollak, Schwartz & Stonestreet, 1979). In contrast, obligate glucose utilizing tissues such as the brain, peripheral nerves, blood components, bone marrow, and renal medulla continue to use glucose as their primary fuel source regardless of the serum glucose concentration (Greenberg, 1973). Although ketones, glycerol and lactate can support cerebral metabolism during periods of extreme hypoglycemia, the brain, a rapidly and highly perfused organ, requires a minute-to-minute supply of glucose. The major portion of basal hepatic glucose output goes to the maintenance of cerebral metabolism (Cornblath &

Schwartz, 1976; Greenberg, 1973).

Serum glucose concentration reflects the dynamic equilibrium between peripheral glucose utilization and hepatic glucose production. In turn, a number of factors determine the capacity of the liver to release glucose into the hepatic vein:

1. Extent of preformed glucose stores.
2. State of multienzyme systems which facilitate glucose production.
3. Secretion of hormones which regulate the rate of glucose production from other substrates.
4. Availability of substrates (derived largely from peripheral tissues) (Greenberg, 1973).

A basic appreciation of these metabolic processes is necessary in order to understand glucose homeostasis.

Glucose Transport and Phosphorylation

The mechanism by which glucose is transported across cell membranes and also transplacentally is facilitated diffusion (Guyton, 1977; Haymond & Pagliara, 1979). This type of diffusion allows movement of molecules from an area of higher concentration to one of lower concentration at a faster rate than would be predicted on just a physical basis. The diffusion is "facilitated" in that a given substance (glucose) combines with a carrier substance in the cell membrane and this carrier-substrate complex

crosses the membrane faster than the substrate alone. Insulin facilitates this transmembrane movement of glucose.

Quantitatively, there is a maternal-to-fetal transfer of approximately six mg/kg/min (fetal weight) of glucose (Haymond & Pagliara, 1979). This maintains the fetal blood glucose concentration in the range of 70-80% of maternal serum values (Cornblath & Schwartz, 1976; Cowett et al., 1979; Miranda & Dweck, 1977). In comparison, the term neonate has a reported basal hepatic output of approximately six to eight mg/kg/minute (Adams, King & Schwartz, 1968; Cowett et al., 1979). In the adult, endogenous hepatic glucose production is closer to two to four mg/kg/minute (Cornblath & Schwartz, 1976).

Whether the source of glucose is endogenous or exogenous, it must first be intracellularly transformed into a more useful form (glucose-six-phosphate) in a process called phosphorylation. Two enzyme systems catalyze this process: a) glucokinase, which is present only in the liver and is insulin dependent, and b) hexokinase, which is present in the liver and all other tissues and is insulin independent. The phosphorylation of glucose is almost completely irreversible except in liver, renal and intestinal

epithelial cells in which specific phosphatases exist that can reverse this process (Guyton, 1977). This presumably accounts for the relative stability of the otherwise diffuseable intracellular glucose molecule.

The fetal and neonatal liver differs from that of the adult in that hexokinase is the only phosphorylating enzyme present (Adams, 1971). With the limited maximum catalyzing capacity of hexokinase and the absence of glucokinase, there is a relatively small, but constant glucose uptake and storage in the fetal and neonatal liver. This could account for the fact that glucose uptake occurs in this population even in the absence of significant insulin responses to a glucose load (Cowett, Susa, Oh & Schwartz, 1978; Fisher, Arrington & Beard, 1977; Pollak, Cowett, Schwartz & Oh, 1978; Varma, Nickerson, Cowan & Hetenyi, 1973).

After phosphorylation, glucose can be utilized via three major pathways:

1. The glycolytic pathway: an immediate energy source.

2. The glycogenesis-glycogenolysis pathway: a stored energy source.

3. The gluconeogenic pathway: a basis for the synthesis of glucose from noncarbohydrate sources (Adams, 1971; Guyton, 1977; Stanley, 1981).

Glycolysis

Glycolysis is the intracellular process which converts glucose into an immediate energy source in the form of ATP (adenosine triphosphate). Glucose-six-phosphate is phosphorylated into fructose-six-phosphate, which then undergoes several successive steps of chemical reactions, each step catalyzed by at least one specific protein enzyme (Figure 1). The end product, after the release of energy, is dependent on the availability of oxygen. In the presence of oxygen, glucose releases energy and pyruvic acid. When oxygen is unavailable or insufficient, a small amount of energy can still be released through glycolysis, resulting in energy and lactic acid. Of the two methods, the aerobic degradation of glucose is much more energy efficient than the anaerobic pathway (Guyton, 1977).

Glycogenesis-Glycogenolysis

Glycogen is the storage form of glucose produced in a process known as glycogenesis. Early in human gestation, the pattern of glycogen metabolism varies from tissue to tissue. The liver, a primary neonatal storage site for glycogen (Cornblath & Schwartz, 1976; Miranda & Dweck, 1977), appears to be a major source of glucose during the time immediately following birth.

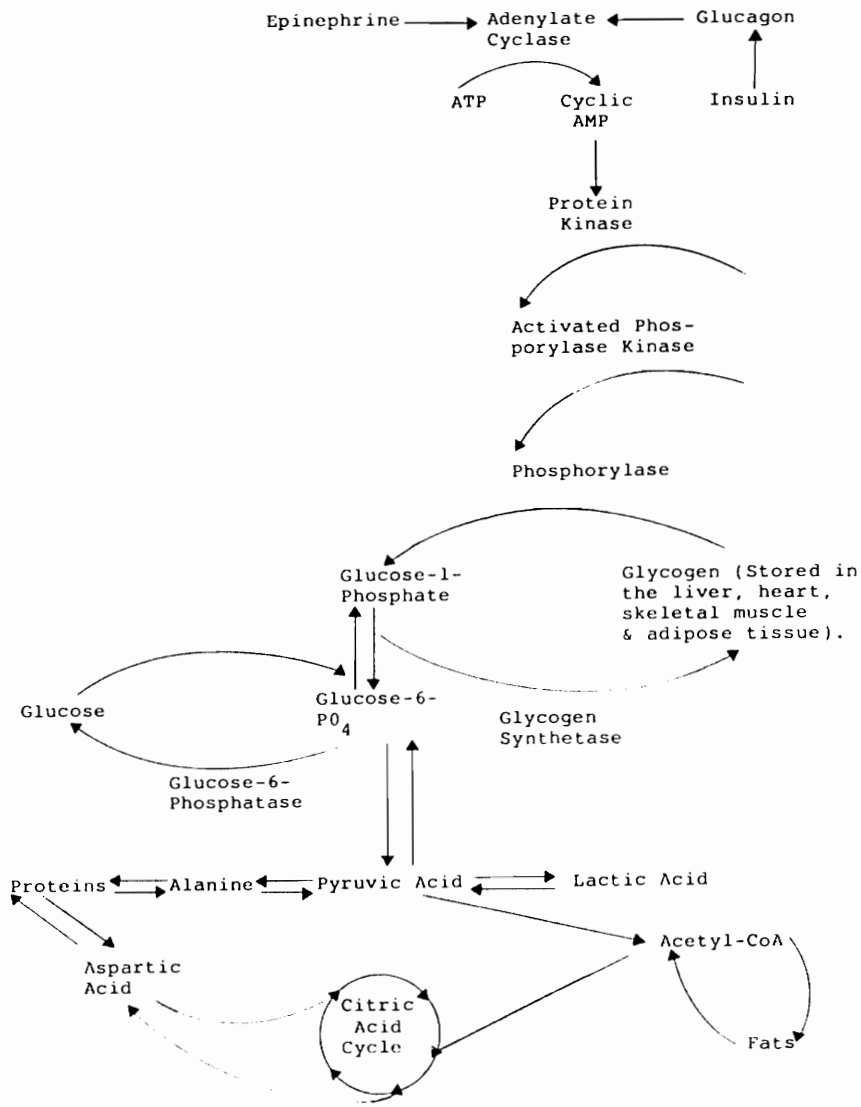

Figure 1. Pathways of glucose metabolism. Adapted from Ganong, 1977.

A variety of hormones is involved in glucose homeostasis. Glucagon is produced by the alpha cells of the pancreatic islets of Langerhans in response to low glucose levels in the blood perfusing the alpha cells. Epinephrine is a catecholamine released by the adrenal medulla, particularly during times of stress. Both of these hormones have been demonstrated to stimulate adenyl cyclase activity which increases the concentration of cyclic AMP, and activates protein kinase in the liver cells (Guyton, 1977). The end result of this cascade of events is the activation of phosphorylase, the enzyme facilitating glycogenolysis, and the inactivation of glycogen synthetase, the enzyme needed for glycogenesis (Adams, 1971; Cornblath & Schwartz, 1976; Haymond & Pagliara, 1979; Stanley, 1981).

Glycogenolysis involves glycogen metabolism into glucose-six-phosphate which can be utilized for energy via the glycolysis pathway. This mechanism of glycogen degradation can only occur in the liver, kidney and intestines which contain the necessary enzymes for breakdown (Guyton, 1977; Haymond & Pagliara, 1979).

Insulin is a hormone which stimulates glycogenesis by inactivating phosphorylase and activating glycogen synthetase. Insulin accomplishes this task by antago-

nizing the effect of glucagon, epinephrine, and cyclic AMP on hepatic glycogen metabolism. The beta cells of the pancreatic islets of Langerhans secrete insulin in response to elevated blood glucose levels. Glucose diffusion into the cell is "facilitated" by insulin in various tissues such as the muscle, connective and adipose tissue. In the liver, however, glucose transport can occur independent of circulating insulin levels (Guyton, 1977; Haymond & Pagliara, 1979). Glucose-six-phosphate is converted into glycogen through a series of enzymatically controlled steps and stored in the liver, heart, skeletal muscle and adipose tissue (Cornblath & Schwartz, 1976).

Gluconeogenesis

Neonatal glycogen stores are rapidly mobilized and are largely depleted within a few hours following birth to meet newly acquired extrauterine needs (i.e., muscular activity, temperature, respiratory and metabolic regulation) (Greenberg, 1973; Miranda & Dweck, 1977). For the premature and, particularly the small-for-gestational age (SGA) infant, availability of glucose from their limited glycogen stores are reduced. Infants, especially when growth retarded and/or subjected to perinatal/neonatal stress, must sustain a relatively increased basal hepatic glucose output

(Miranda & Dweck, 1977). Following the depletion of glycogen stores, the supply of glucose by the liver is dependent on gluconeogenesis (Adams, 1971; Haymond & Pagliara, 1979; Stanley, 1981).

The pathway for the synthesis of glucose from various other substrates is present in the liver, kidney and intestines (Stanley, 1981). The liver is the major organ of gluconeogenesis using lactate, glycerol and amino acids (alanine) as the precursors for glucose production. The rate of gluconeogenesis in the liver is stimulated by glucagon, catecholamine and glucocorticoids and inhibited by insulin. Only after prolonged fasting is the kidney's importance as a gluconeogenic organ realized. In the kidney, the amino acid glutamine replaces alanine as an important precursor for glucose (Haymond & Pagliara, 1979; Stanley, 1981). During nonacidotic conditions, the small intestines absorb glutamine released by skeletal muscles. The small intestines in vivo utilizes glutamine as its own respiratory substrate as well as converting it into alanine for hepatic gluconeogenesis (Stanley, 1981).

Hyperglycemia

While the frequency and clinical importance of hypoglycemia has been well documented, the incidence

of hyperglycemia may also be a significant problem of the preterm neonate (Cornblath & Schwartz, 1976; Cowett et al., 1979; Miranda & Dweck, 1977; Zarif, Pildes & Vidyasagar, 1976). Originally, neonatal hyperglycemia was recognized as transient neonatal diabetes mellitus (Gentz & Cornblath, 1969). The spontaneously reversible deficiency of insulin secretion or the production of a biologically inactive form of insulin remains the hallmark of this disease (Cornblath, 1977; Gentz & Cornblath, 1969). This abnormal insulin secretion is suggestive of a delayed or abnormal maturation of pancreatic beta-cells and/or absence of inhibitors of pancreatic alpha cells in response to glucose infusion (Sodoyez-Goffaux & Sodoyez, 1977). Studies have documented neonatal hyperglycemic episodes in association with exogenous glucose infusions (Heird, Driscoll, Schullinger, Grebin & Winters, 1972; Zarif et al., 1976). This glucose intolerance is more prominent in the small-for-gestational-age (SGA) infant (Dweck & Cassady, 1974). The reported hyperglycemia of the SGA infant following parenteral infusion of glucose is more likely to occur in the first 24-48 hours of life (Cowett et al., 1979; Dweck & Cassidy, 1974; Zarif et al., 1976) and is significantly more common at intravenous infusion

rates exceeding six mg/kg/minute (Cowett et al., 1979; Dweck & Cassady, 1974).

The adult response to a small intravenous glucose infusion is a slightly elevated plasma insulin level with a decrease in glucose production and an increase in peripheral glucose uptake (Sacca, Vitale, Cicala, Trimarco & Ungaro, 1981). In comparison to their adult counterparts, the preterm infant may not have these abilities to respond to a glucose load. The small preterm infant seems to be less able to turn off endogenous glucose production when exogenous glucose sources are provided (Sherwood & Chance, 1977). The preterm infant has the capacity to secrete insulin (Baum & Porte, 1980; Cowett et al., 1979; Salle & Ruitton-Uglienco, 1976). In fact, documentation of a brisk surge of insulin release can be stimulated by the infusion of intravenous amino acids (Fisher, 1975). Following a glucose infusion, a similar response of serum hyperinsulinemia can be obtained; however, serum glucose levels do not return toward normal values in response to this increase in insulin (Pollak et al., 1978; Zarif et al., 1976). Some suggest that the insulin rise is inappropriately low in comparison to the degree of hyperglycemia observed. Immature function of the pancreas, causing a slower response

of the beta-cells has been postulated to cause this discrepancy in serum insulin and glucose levels (Zarif et al., 1976). This is supported by the fact that administration of supplemental insulin will facilitate a decrease in serum glucose values (Pollak et al., 1978). The inappropriate response to insulin may also reflect an ineffective delivery of insulin to the periphery or a decrease in sensitivity of peripheral tissues to insulin. Reports of peripheral plasma insulin responses are extremely variable and seem to show no correlation to plasma glucose levels (Pollak et al., 1978). This fine control of glucose homeostasis in the preterm infant may require a higher insulin level to effectively lower endogenous hepatic output and/or enhance glucose utilization. Cowett and colleagues (1979) reported the responsiveness of end organ sensitivity to insulin may be the problem involved with glucose intolerance. A smaller mass of insulin-sensitive tissue (adipose tissue) of the very immature infant supports this thought (Pollak et al., 1978). It has also been hypothesized that the decreased response to insulin may be a result of an immature enzyme system (Goldman & Hirata, 1980).

Growth hormone has varying effects on the neonate's response to plasma glucose and insulin levels.

Growth hormone stimulates protein synthesis and cell multiplication during periods of adequate nutrition (i.e., adequate calories, amino acids, and insulin levels). In fasting states, growth hormone levels increase while decreasing glucose uptake and stimulates fat mobilization, providing substrates for gluconeogenesis (Fletcher, 1981). Although the physiologic role of growth hormone in the human fetus is not clearly defined, it is not necessary for fetal growth (Adams, 1971). Several factors favor the conclusion that increased growth hormone levels during the first few days of neonatal life do not contribute to glucose intolerance:

1. Neonatal serum growth hormone levels are elevated for the first few days of life (premature and full-term infants), regardless of serum glucose values or exogenous glucose supplementation (Fletcher, 1981; Zarif et al., 1976).

2. There exists a paradoxical response of plasma growth hormone to an exogenous glucose load, showing a rise rather than a fall. This is a temporary pattern and disappears after the first few days of life (Adams, 1971; Zarif et al., 1976).

3. Growth hormone values among hyperglycemia and normoglycemic infants do not differ (Zarif et al., 1976).

Stress has been identified as another significant factor responsible for hyperglycemia (Lilien, Rosenfield, Baccaro & Pildes, 1979; Rizza, Cryer, Haymond & Gerich,

1980; Sherwood & Chance, 1977; Zarif et al., 1976). Stress leads to excessive adrenergic activity resulting in increased circulating cortisol and/or catecholamine secretion. It has been reported that among premature infants with respiratory distress syndrome, those less than or equal to 32 weeks gestation had higher concentrations of corticosteroids than those greater than 32 weeks (Baden, Bauer, Colle, Klein, Papageorgiou & Stern, 1973). This would suggest an exaggerated response to stress or an attenuated ability to metabolize these hormones. Catecholamine levels in the stressed term and preterm infant demonstrate an intact sympathetic-adrenal system. Catecholamines (epinephrine and norepinephrine) rapidly mobilize glycogen stores through glycogenolysis, stimulate gluconeogenic substrates in the skeletal muscle and adipose tissue, decrease glucose clearance, and suppress pancreatic insulin output while augmenting glucagon secretion (Guyton, 1977).

Stress hyperglycemia can result from a variety of predisposing conditions. Baum and Porte (1980) proposed that a series of interrelated events, triggered by an acute hypoxemic episode and mediated by the sympathetic nervous system, stimulate adrenergic receptors and resulting in hyperglycemia (Figure 2).

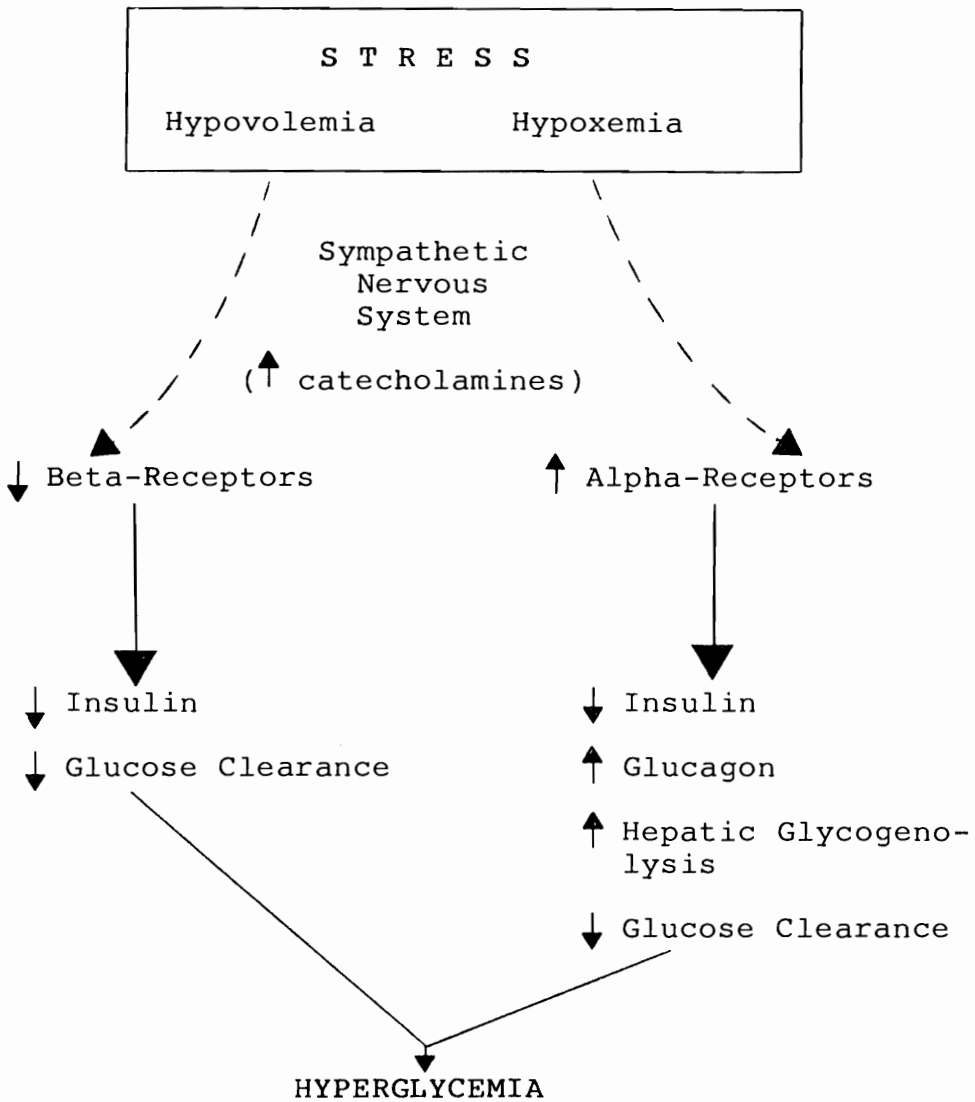

Figure 2. A proposed mechanism for stress hyperglycemia.

A fall in arterial oxygen tension to levels less than 30 torr, stimulates the alpha and beta adrenergic receptors. Alpha adrenergic stimulation is critical to hepatic glycogenolysis and is a major contributor to the inhibition of insulin release in acute hypoxemia. In this study, hypoxia was also shown to cause a beta receptor dysfunction, resulting in alpha receptor domination, further promoting glucagon and inhibiting insulin release. Glucose clearance is also decreased due to the elevated circulating levels of catecholamines stimulated by the stress of the hypoxemia. The combination of these events result in hyperglycemia.

Hyperglycemia has been reported in association with various shock syndromes (Cerchio, Persico & Jaffay, 1973; Cryer, Herman & Sode, 1971; James, 1979). Inadequate insulin response during an acute hypovolemic episode (Figure 2) was postulated as the major contributing factor of hyperglycemia by James (1979). The inhibitory effects of catecholamines on pancreatic beta cells, resulting in inadequate insulin release, promotes glucose production and suppresses glucose clearance (Cerchio et al., 1973; Grajwer, Sperling, Sack & Fisher, 1977; Rizza et al., 1980). This response was reported as being primarily a beta adrenergic mechanism, whereas in hypoxemia, alpha

adrenergic responses predominate (Baum & Porte, 1980; Rizza et al., 1980). These apparently paradoxical findings suggest that the adrenergic mechanisms depend upon the specific nature of the stress-provoking condition (Johnson & Ensinck, 1976).

The three anti-insulin hormones, glucagon, cortisol and epinephrine, when considered individually, result in a transient and often mild increase of the blood glucose concentration (DeFonzo, Sherwin & Felig, 1980; Shamoon, Hendler & Sherwin, 1981). These studies suggest that stress hyperglycemia cannot be ascribed to a single hormone, but is a consequence of the synergistic interactions among these counter-regulatory hormones. Glucose overproduction is stimulated by glucagon and epinephrine, and sustained by elevated cortisol levels (Shamoon et al., 1981). Insulin levels in the normal subjects of this study demonstrated an increase over baseline, but not in direct correlation with the degree of hyperglycemia. This study suggests that a preexisting abnormality in insulin secretion is not required for the stress hyperglycemia potentiated by the three anti-insulin hormones (DeFonzo et al., 1980; Shamoon et al., 1981).

Many believe that the dangers of hyperglycemia in the preterm neonate relate to changes in serum

osmolality (Dweck, 1976; Finberg, 1967). Each 18 mg/dl increase in blood glucose concentration results in a 1 MOsm/liter increase in serum osmolality. The hyperosmolality caused by an increase of greater than 25-40 mOsm/liter (>250 to 400 mg glucose/100 ml blood) can result in a number of potentially deleterious consequences. The hazards of a sustained state of hyperosmolality may produce brain cell dysfunction, osmotic diuresis with subsequent dehydration, and expansion of vascular volume with capillary dilatation possibly contributing to a periventricular-intraventricular hemorrhage (Arant & Gooch, 1979; Dweck, 1976; Dweck & Cassady, 1974; Finberg, 1967). The maximum safe tolerance in serum osmolality increase is suggested to be approximately 25 mOsm per liter of water (250 mg/100 ml) over four hours (Finberg, 1967). However, if sustained, even this degree of rise may result in any of the above complications (Dweck & Cassady, 1974; Zarif et al., 1976).

Periventricular-Intraventricular Hemorrhage

Periventricular-intraventricular hemorrhages have been reported to originate from the subependymal germinal matrix (Hambleton & Wigglesworth, 1976; Volpe, 1981). This region consists of the ventricular

and subventricular zones found in every level of the developing central nervous system, from which all neurons and supporting glia originate.

The germinal matrix of those infants up to 32 weeks gestation is described as a capillary bed consisting of a network of interlacing blood vessels (Hambleton & Wigglesworth, 1976). Heubner's artery, a branch of the anterior cerebral artery as well as the lateral striate and the anterior choroidal artery provide the major blood supply to the germinal matrix-basal ganglia area. The relative large size of these vessels supports a substantial portion of cerebral blood flow during the critical period of neuronal proliferation (Hambleton & Wigglesworth, 1976; Takashima & Tanaka, 1978; Volpe, 1981).

The venous drainage system is provided through the terminal, choroidal and thalamostriate veins which course anteriorly and converge near the foramen of Monro and the head of the caudate nucleus forming the internal cerebral vein. The direction of flow takes a sudden U-turn at this point and the internal cerebral vein then courses posteriorly to eventually terminate in the Great Vein of Galen (Friede, 1975; Takashima & Tanaka, 1978; Volpe, 1981; Wigglesworth & Pape, 1980). The sharp angle at this junction has

been suggested to be a particularly vulnerable zone for hemorrhage into the germinal matrix (Larroche, 1964).

Previous studies in search of the origin of hemorrhage centered around the arteries and veins of the germinal matrix systems, primarily the terminal vein (Grontoft, 1953). Recent studies show a disruption of the microcirculation of the immature capillary bed as the origin of PV-IVH, rather than rupture of the terminal vein or its branches (Hambleton & Wigglesworth, 1976). Although subependymal hemorrhages can occur wherever there is germinal matrix, there are recognizable relationships to gestational age and site of rupture within the matrix. Hemorrhages of the very immature infant (less than or equal to 28 weeks gestation) were primarily over the body of the caudate nucleus, lateral to the body of the thalamus. The origin of PV-IVH in neonates 28-30 weeks gestation was predominantly over the head of the caudate nucleus adjacent to the foramen of Monro (Hambleton & Wigglesworth, 1976; Leech & Kohnen, 1974). The choroid plexus appeared to be the site of original rupture in infants greater than 30 weeks gestation (Donat, Okazaki, Kleinberg & Reagan, 1978).

Pathogenesis

Various mechanisms have been attributed to the etiology of PV-IVH in the sick preterm infant. The structural and histological immaturity and characteristic vascular architecture of the large subependymal-germinal matrix are factors predisposing the preterm infant to a periventricular-intraventricular hemorrhage (Gruenwald, 1951; Hambleton & Wigglesworth, 1976; Towbin, 1968; Wigglesworth & Pape, 1980). Cells migrate from the subependymal germinal matrix outward to form the layers of the cerebral cortex and deeper nuclear structures (Friede, 1975). The germinal matrix only begins to thin out at about 30 weeks gestation (Friede, 1975). This gelatinous matrix provides poor support for the capillaries and veins of this area thereby increasing their susceptibility to mechanical forces generated by intravascular pressure changes (Cole, Durbin, Olaffson, Reynolds, Rivers & Smith, 1974; Cooke, Rolfe & Howat, 1979; Ross & Dimmette, 1965; Dykes, Lazzara, Ahmann, Blumenstein, Schwartz & Brann, 1980; Volpe, 1981; Wigglesworth & Pape, 1980). Pressure changes implicated in the pathogenesis of PV-IVH include increase in central venous pressure (Cole et al., 1974; Dykes et al., 1980; Leech & Kohnen, 1974; Ross & Dimmette, 1965), increase in mean arterial blood pressure

(Cooke et al., 1979; Ment, Ehrenkranz, Lange, Rothstein & Duncan, 1981; Wigglesworth & Pape, 1980), and/or alterations in the autoregulatory mechanisms of cerebral blood flow (Dykes et al., 1980; Lou, Lassen & Friis-Hansen, 1977; Ment et al., 1981).

Asphyxia is the primary cause of increased venous pressure because it creates severe venous congestion and thrombus formation. This results in focal infarctions in the subependymal area and eventual rupture of the thin-walled vessels of the germinal matrix (Grontoft, 1953; Gruenwald, 1951; Larroche, 1964; Leech & Kohnen, 1974; Ross & Dimmette, 1965; Towbin, 1968). Hypoxic myocardial insufficiency secondary to asphyxia associated with respiratory distress of the premature contributes to this vascular disturbance (Cole et al., 1974).

Under normal conditions, changes in cerebral vascular tone maintain cerebral blood flow within a constant narrow range regardless of wide variations in arterial blood pressure (Lou et al., 1977; Raju, Doshi & Vidyasagar, 1982). However, in the distressed newborn, a faulty autoregulatory mechanism results in a "pressure-passive" form of cerebral perfusion (Fujimura et al., 1979; Lou et al., 1977; Ment et al., 1981). Impaired vascular autoregulation results in

maximal cerebral vasodilatation (Lou et al., 1979). Volume expansion and/or sudden rises in mean arterial blood pressure following periods of relative hypotension can result in "luxury perfusion" to the subependymal germinal matrix area (Fujimura et al., 1979). Recent anatomic data indicating the capillaries as the origin of PV-IVH, support the notion that as arterial pressure rises, capillaries in the poorly supported germinal matrix may rupture (Cooke et al., 1979; Hambleton & Wigglesworth, 1976; Lou et al., 1979). The hypotension resulting in decreased cerebral perfusion could also lead to infarction of the germinal matrix capillary bed. Any subsequent increase in cerebral blood flow or increase in intravascular pressure could rupture the damaged microvasculature and lead to hemorrhage (Dykes et al., 1980).

Others have also proposed a hypothesis of lowered cerebral tissue pressure as a factor leading to PV-IVH. The intravascular pressure acting on the vessel wall and the tissue pressure existing outside the vessel are the primary forces involved. If this transmural pressure gradient from the intravascular to extravascular space becomes excessive, hemorrhage can result (Milnor, 1980). This excessive pressure gradient can occur with an increase in intravascular

pressure, a decrease in tissue pressure or a combination of both acting together. Although most studies reflect the view that either an increase in arterial or venous pressure is a major factor in PV-IVH (Cole et al., 1974; Connor, Lorenzo, Welch & Dorval, 1983; Grontoft, 1953; Hambleton & Wigglesworth, 1976; Ross & Dimmette, 1965; Wigglesworth & Pape, 1980), a reduced tissue pressure can also contribute significantly to the development of hemorrhage (Coulter, 1980; de Courten & Rabinowicz, 1981).

Tissue pressure varies directly with water content. Therefore, any condition which will decrease brain tissue water results in lowered cerebral tissue pressure. Plasma hyperosmolality resulting from dehydration, hypernatremia, hyperglycemia or infusion of hypertonic solutions will result in this type of water movement (de Courten & Rabinowicz, 1981; Papile, Burstein, Burstein, Koffler & Koops, 1979; Thomas, 1981). Any situation which will decrease vascular filtration pressure (i.e., hypovolemia, hypotension) will also reduce water movement into the tissues (Connor et al., 1983; Milnor, 1980). A sudden increase in blood pressure in the face of lowered tissue pressure, particularly in the gelatinous, poorly supported matrix area, may readily result in rupture

and hemorrhage (Goldstein, 1979; Lou et al., 1977).

Water volume loss in the preterm infant brain tissue during the first 24-48 hours of life has been reported (Williams, Chir, Hirsch, Corbet & Rudolf, 1977). This brain shrinkage was inferred because of a direct correlation between decreased head circumference, loss of body weight and decreased serum sodium levels. Supporting this observation, Welch (1980) reported a gradual decline in intracranial pressure during this same time period in a comparable population of infants. However, an alternative explanation for smaller head measurements may be a decrease in cerebrospinal fluid volume. Another study directly assessing brain tissue hydration reported a direct correlation of brain water content to weight gain at 72 hours of age (Coulter & Avery, 1980). Brain tissue from subjects gaining less than 30% of their birthweight contained less water than those gaining greater than 30% of their birthweight.

Thomas (1976) demonstrated a direct relationship between hyperosmolality and the occurrence of PV-IVH. Although there was no significant correlation between serum sodium levels and serum osmolality values, infants who died with PV-IVH demonstrated, at some time prior to death, an osmolality value exceeding

two standard deviations above the mean compared to those without a PV-IVH (Thomas, 1976). In humans, approximately half of the plasma osmolality is due to sodium ions (Walker & Whelton, 1980). Therefore, a rise in serum sodium concentration would understandably lead to an increase in serum osmolality values. This, however, is not the case with neonates. Increased serum osmolality values were associated with very low sodium concentrations. This finding would suggest the possibility of other molecules capable of increasing serum osmolality exerting an effect. Erdem, Gogus, Tuncer and Demisoy (1979) suggest that hyperglycemia may contribute to the hyperosmolality which may potentially lead to an intraventricular hemorrhage. Because the relationship between the variables hyperglycemia and PV-IVH seem to be related but have not been specifically investigated, it was this researcher's intent to explore this relationship further. To establish a correlation between the development of hyperglycemia and the occurrence of PV-IVH could potentially guide future investigations.

Clinical Features

Prior to the age of computerized tomography (CT) and ultrasound scanning, most PV-IVH were discovered on necropsy (Cooke, 1981; Kaplan, Ben-Ora, Hart &

Meyer, 1981). Employing these advanced techniques for in vivo observation of the cerebral structures has identified many cases of PV-IVH which would previously have gone unrecognized. Various associated risk factors have been identified as predisposing an infant to hemorrhage such as prematurity, gestational age, birthweight, Apgar score, sex, and respiratory distress (de Courten & Rabinowicz, 1981; Levene et al., 1982; Schoenberg et al., 1977). Recently the effects of sodium bicarbonate infusion, mechanical ventilation, pneumothoraces and neonatal fluid balance have been named as factors associated with PV-IVH in these preterm infants (Goldstein, 1979; Hill, Perlman & Volpe, 1982; Levene et al., 1982; Thomas, 1976).

Clinically, symptoms associated with a sudden deterioration in the cardiopulmonary status of an infant, (e.g., rapid deterioration, seizures, coma, as well as a more subtle presentation, e.g., altered state of consciousness, subtle aberrations in eye movement, gradual disturbances in respiratory function), lead to suspicion of a recent PV-IVH. Whether catastrophic or subtle, the presence of the above symptoms in conjunction with an unexplained drop in hematocrit, an inability to raise the hematocrit with a blood transfusion and/or a tight, bulging fontanel

(Lazzara et al., 1980) should lead to questions and investigation of a possible PV-IVH.

Diagnosis and Management

Accurate diagnosis of PV-IVH has become an increasingly greater concern as neonatal care of preterm infants has improved. The need for a portable and noninvasive means for the detection and management of PV-IVH has been investigated. Real-time ultrasound provides a practical and efficient means of monitoring this intracranial lesion. Comparative studies of CT and ultrasound methods of detecting PV-IVH have shown excellent correlation in anatomic location, extent of hemorrhage, and the degree of ventricular dilatation (Kaplan et al., 1981; Sauerbrei, Digney, Harrison & Cooperberg, 1981). Ultrasonic imaging has facilitated monitoring and management of PV-IVH as well as furthering knowledge in the etiology of this lesion.

The ultimate in management of PV-IVH would be the prevention of these lesions. However, until the delivery of preterm infants can be eliminated and/or the etiology of PV-IVH and its prevention can be determined, health care personnel are faced with both acute and longterm supportive care planning. Acute management includes supporting cardiopulmonary and metabolic status, the maintenance of cerebral perfusion

and avoidance of cerebral overperfusion (Volpe, 1981). Careful follow-up and monitoring for posthemorrhagic sequelae can be achieved rapidly and efficiently with the use of ultrasound. The most common long-term neurologic problems encountered after a PV-IVH are hydrocephalus, parenchymal damage and development of porencephaly (Kaplan et al., 1981; Volpe, 1981). Studies have revealed that the quantity of bleeding may have prognostic value in regards to the development of posthemorrhagic hydrocephalus (Ahmann et al., 1980; Papile, Burstein, Burstein, Koffler, Koops & Johnson, 1980). Recent studies, based on both neurologic examination and developmental testing, report the incidence of abnormal outcome related to extreme prematurity (less than or equal to 27 weeks gestation) as well as severity of the initial hemorrhage (Williamson, Desmond, Wilson, Andrew & Garcia-Prats, 1982).

Hydrocephalus exists when there is an imbalance between cerebral spinal fluid (CSF) production and absorption. In PV-IVH, hydrocephalus is primarily due to abnormal absorption resulting from obstruction of the outflow tract and from impairment of the reabsorptive surface secondary to arachnoiditis. Obstruction is dependent upon pressure and tissue compliance (Ahmann et al., 1980). Both of these factors are

influenced by the developmental state of the preterm infant's intracranial structures which allow compression of cerebral white matter at pressures lower than those needed to overcome the restrictions of the dura and skull (Volpe, 1981). Papile et al., (1980) reported success with serial lumbar punctures to arrest progressive ventricular dilatation, lower CSF pressure and facilitate CSF absorption by removing blood and protein. Other researchers report that, in most cases, spontaneous resolution of ventricular dilation is observed even without intervention (Levene & Starte, 1981).

Cerebral compression resulting in brain injury due to progressive ventricular dilatation may occur days to weeks before the appearance of traditional clinical features of splitting cranial sutures, bulging anterior fontanelle and rapidly increasing head growth (Volpe, Pasternak & Allen, 1977). This delay in detection and treatment may be an important determinant in the poor neurological outlook in PV-IVH (Papile et al., 1980; Volpe et al., 1977). Early intervention to lessen brain injury (i.e., axonal swelling and disruption) is now possibly due to CT and ultrasound scanning techniques. Clinical features helpful in prognosticating the outcome from PV-IVH could also

guide the management and follow-up from this hemorrhagic event. Merguerian, Perel, Wald, Feinsod, and Coter (1981) reported that persistent hyperglycemia was a grave prognostic sign in adult head-injured patients. This study will also investigate hyperglycemia in the preterm infant in relation to the existence and extent of a periventricular-intraventricular hemorrhage.

Research Questions

The research questions addressed in this study were:

1. Does hyperglycemia occur in relation to the onset of clinical signs of PV-IVH?
2. Is the degree of glucose intolerance reflective of the grade of PV-IVH?
3. Is the degree of hyperglycemia, regardless of the grade of the PV-IVH, related to the development of posthemorrhagic hydrocephalus?

Definition of Terms

1. Periventricular-intraventricular hemorrhage (PV-IVH) was defined as hemorrhage into the region of the terminal vein of the subependymal germinal matrix. This lesion is graded by severity (Papile et al., 1978) as follows:
    a. Grade I-a subependymal hemorrhage
    b. Grade II-an intraventricular hemorrhage, without ventricular dilatation
    c. Grade III-an intraventricular hemorrhage with ventricular dilatation

d. Grade IV-an intraventricular hemorrhage with ventricular dilation plus parenchymal extension of the hemorrhage.

2. A premature infant was considered neonate born at less than or equal to 37 weeks gestation.

3. Gestational age was defined as the post-conceptual age of a fetus/neonate and was determined by admission physical examination.

4. Posthemorrhagic ventricular dilatation was considered as ultrasonographic diagnosis of enlarged ventricles following a PV-IVH.

5. A posthemorrhagic hydrocephalus was defined as a progressive enlargement of the ventricles with abnormal head growth, requiring surgical placement of a ventriculo-peritoneal shunt.

6. Hyperglycemia was defined as a serum glucose value greater than or equal to 120 mg/dl.

   a. Hypoglycemia = $\leq$ 39 mg/dl

   b. Euglycemia = 40-120 mg/dl

   c. Mild hyperglycemia = 121-169 mg/dl

   d. Moderate hyperglycemia = 170-210 mg/dl

   e. Severe hyperglycemia = 211-249 mg/dl

   f. Very severe hyperglycemia = $\geq$ 250 mg/dl.

7. Ventilatory support was defined as infants requiring endotracheal intubation and attachment to a mechanical ventilator.

   a. Minimum support = CPAP and/or IMV $\leq$ 10 and/or pressures 18/3

   b. Mild support = IMV $\leq$ 20 and/or pressures $\leq$ 25/5

   c. Moderate support = IMV $\leq$ 30 and/or pressures $\leq$ 30/5

d. Maximum support = IMV $\geq$ 31 and/or pressures $\geq$ 31/6.

8. Stress was considered a disturbance in the component(s) of a system resulting in a dysfunction or disorganization of the system.

Assumptions

The assumptions in this research study were:

1. A disturbance or stress has been imposed on the system which is reflected in hyperglycemia.

2. Hyperglycemia causes additional stress on a system.

3. PV-IVH is preceded by a system disturbance.

4. The clinical signs potentially associated with PV-IVH can be determined from the examination of the progress notes and/or nurses notes of the medical records.

CHAPTER III

METHODOLOGY

Design

The design of this study was an ex post facto, descriptive correlational investigation. Ex post facto research allows the investigator to systematically examine relationships among variables (Polit & Hungler, 1978; Waltz & Bausell, 1981). This design is often utilized in research studies involving human beings for the following reasons:

1. The complexity of interacting variables involved in maintaining homeostasis among the various subsystems of the human body.
2. The nature of the independent variable involved is such that its manipulation could potentially cause physical harm to the subject.
3. Constraining situations (i.e., insufficient time, inconvenience, lack of cooperation, and/or lack of adequate funds) may make a true experiment nonpractical (Polit & Hungler, 1978).

A content analysis of patient medical records was performed to investigate the independent variable of hyperglycemia as a factor involved with periventricular-intraventricular hemorrhages of the preterm infant.

Retrospective studies cannot infer a causal relationship. However, the identification of a correlation between the independent variable and the dependent variable under study could direct further research.

The time series analysis (Campbell & Stanley, 1963) is an ex post facto design in which there is a periodic measurement (Dextrostix® determinations) on a group and the introduction of an experimental change or the occurrence of a natural event (PV-IVH) into this time series of measurements (Campbell & Stanley, 1963). The (dis)continuity in the recorded Dextrostix® measurements (0_1-0_8) in the time series before and after the PV-IVH (X) will be compared in an attempt to identify the effect of X (Figure 3).

Threats to internal validity which may offer alternative explanations for the (dis)continuity of the serial measurements need to be addressed. Failure to control for history is a weakness of this design (Campbell & Stanley, 1963). A simultaneously occurring event, other than X, may result in these discontinuous measurements as well. Awareness of rival events known to cause hyperglycemia and exclusion of subjects affected by these events from the study lends greater credence to the interpretation of obtained data.

Instrumentation is another possible confounding

O_1 O_2 O_3 O_4 X O_5 O_6 O_7 O_8*

X = PV - IVH

O_1 to O_4 = pre-PV-IVH Dextrostix®

O_5 to O_8 post-PV-IVH Dextrostix®

Figure 3. Research design. (*Notation developed by Campbell & Stanley, 1963).

variable associated with this design (Campbell & Stanley, 1963). Inaccurate usage of the various instruments utilized in determining: 1) Dextrostix® reading and 2) PV-IVH grading, could be misinterpreted as being the effect of X. This factor is even more prevalent in an ex post facto chart analysis. Knowledge of skill, technique and experience of individuals performing the Dextrostix® readings and the ultrasound imaging is not readily accessible.

Another weakness of this study design was the inability to randomize and the inability to manipulate the independent variable. This lack of control results in an increased risk of overinterpretation of the results (Kerlinger, 1973).

Despite its weaknesses, ex post facto correlational studies are advantageous in many research situations in which a controlled inquiry is desired but true experimentation is not feasible (Kerlinger, 1973). The design described above can result in an efficient and effective means of investigating a problem area in which the variables involved are very complex and involves the collection of a large amount of data (Kerlinger, 1973; Polit & Hungler, 1978; Waltz & Bausell, 1981). Correlational studies are very strong in realism. The results of a study obtained in a natural setting are

more likely to be generalizable to other similar settings than results obtained in an experimental laboratory setting (Kerlinger, 1973; Polit & Hungler, 1978).

Several studies have examined the various clinical features often associated with PV-IVH (Lazzara et al., 1980; Lilien et al., 1979). Hyperglycemia and PV-IVH in these reports were not found to be significantly correlated. No study investigating the specific variable of hyperglycemia in relation to PV-IVH was discovered in this investigator's review of the literature. However, Erdem et al., (1979) reported one case study and others have speculated how hyperglycemia may predispose preterm infants to this neurologic complication (Arant & Gooch, 1979; Dweck, 1976; Dweck & Cassady, 1974; Finberg, 1967). A retrospective correlational study using content analysis of medical records seems to be an appropriate preliminary research step in identifying the existence of a relationship between the variables in question. A causal relationship cannot be determined by this type of study.

Instruments

Dextrostix

The Dextrostix®, a Miles Laboratory product, is a firm plastic strip which has an area of reagents

employed to determine the amount of glucose in whole blood. The active end of the test strip is impregnated with a glucose-oxidase/peroxidase chromagen mixture and coated with a semipermeable membrane which prevents staining by red blood cells. Glucose from the blood passes through this membrane and initiates the dry-reagent system of glucose oxidation producing characteristic colors of the oxidized chromagens. The intensity of the color is proportional to the glucose concentration in the blood (Miles Laboratory, 1979-80; Moss, 1968; Rennie, Keen & Southon, 1964).

This semiquantitative enzyme-strip method for estimating blood glucose values was first introduced in 1964 (Moss, 1968; Orzeck, Mooney & Owens, 1971; Rennie et al., 1964), and is found an efficient and effective screening tool, when performed by experienced laboratory technologists (Perelman, Gutcher, Engle & MacDonald, 1982). In one minute, this method requiring one drop of blood, provides a visual range of blood glucose levels between zero and 250 mg glucose/dl (Miles Laboratory, 1979; Moss, 1968; Orzeck et al., 1971). However, limitations of this glucose screening method have been identified as follows:

1. Operator variables such as timing, washing and sample application must closely follow directions supplied by Miles Laboratory (1979), in order to obtain reliable results (Moss,

1968; Rennie et al., 1964).

2. Reagent strip deterioration may result from exposure to light, heat and ambient moisture as well as aging of the Dextrostix® resulting in inaccurate values (Miles Laboratory, 1979-80).

3. Observer inexperience in strip/color-chart interpretation may introduce error into the results (Miles Laboratory, 1979-80; Rennie et al., 1964).

4. A number of potentially interfering substances have been identified, such as an elevated hematocrit resulting in a low Dextrostix® reading (Strauchen, Alston, Anderson, Gustafson & Fajardo, 1981), isopropyl alcohol resulting in erroneously high Dextrostix® values (Grazaitis & Sexson, 1980), and the chemical, fluoride, interfering with reagent strip reaction (Miles Laboratory, 1979-80).

5. Dextrostix® under-and-overestimations have been noted at extremely high and extremely low blood sugar levels respectively (Miles Laboratory, 1979-80; Perelman et al., 1982; Rennie et al., 1964).

Dextrometer

The dextrometer is a reflectance colorimeter which quantitatively measures the degree of color change on the Dextrostix® reagent strip (Miles Laboratory, 1979-80). A microcomputer within this compact and portable instrument interprets the electrical signals reflected from the reagent area and digitally displays the resultant glucose value. The manufacturer provides simple calibration methods to continually assure reliable results. Data based upon a dextrometer calibrated with a 130 mg/dl solution

shows an approximate 97% correlation between semi-automated whole blood glucose determination and the dextrometer/Dextrostix® system. This data further demonstrated that dextrometer readings were within 5% of the actual blood glucose concentration within the range of 50-350 mg/dl glucose (Miles Laboratory, 1979-80).

The dextrometer/Dextrostix® method of glucose screening is utilized by the University of Utah Medical Center's NICU. Dextrometer values less than 30 and greater than 130 mg/dl are followed up by chemical blood sugar estimations.

Real Time Ultrasound
Sector Scanner

Ultrasonography is a method of producing two dimensional images of biologic soft tissues using high frequency sound energy. The acoustic property of various bodily tissues is primarily determined by the presence of collagen and fat micelles within the tissues. Therefore, the image is essentially a map of the collagen and fat distribution of the tissue (Field & Dunn, 1973). Structures rich in collagen and fat are more echogenic, whereas liquids containing no collagen or fat are virtually devoid of echoes. The varying intensities of echoes are displayed as shades of gray. The University of Utah Medical Center

utilizes the Advanced Technology Labs Real Time ultrasound sector scanner. This system is suitable for grayscale imaging of cardiac, abdominal and peripheral vascular structures up to a depth of 30 cm (Advanced Technology Labs, 1980).

Two dimensional ultrasound scanning has allowed in vivo visualization of PV-IVH (Cooke, 1981; Kaplan et al., 1981; Levene, Wigglesworth & Dubowitz, 1981). The ultrasound equipment is portable and does not require radiating the patients, thus making this method ideal for studying infants in the NICU.

Sampling and Data Collection Procedures

A nonprobability convenience sample of infants at the University of Utah Medical Center's Newborn ICU was utilized. Subjects were identified by a computer search. The sampling time period encompassed those years in which the diagnosis of PV-IVH was achieved through the use of ultrasonography. Infants to be included in this study will be: a) preterm (less than 37 weeks gestation), b) hyperglycemic, and/or c) diagnosed with PV-IVH during the first seven days of life. Because glucose intolerance has been reported to be associated with infants diagnosed with sepsis and/or

necrotizing enterocolitis, these infants were excluded from the study (Cryer et al., 1971; Lanham, 1982).

CHAPTER IV

RESULTS AND DISCUSSION

The statistical computation was performed by a Sperry Univac 1100 Computer located at the University of Utah Computer Center (Salt Lake City, Utah). The Statistical Package for the Social Sciences (SPSS) (Nie, Hull, Steinbrenner & Brent, 1975) program and the Stat 80 program were utilized for data analysis (Fullerton, 1981). The statistical level of confidence was established at a value of $p \leq 0.05$.

Descriptive Data

Computerized data retrival identified a total of 257 charts of preterm infants (less than or equal to 37 weeks gestation) born between the months of December, 1981 and December, 1982. Of these 257 charts, 102 subjects were identified as having the primary diagnosis of PV-IVH, PV-IVH and hyperglycemia (GH), or hyperglycemia (HG). Four charts were unavailable from the medical records department. Forty-one charts did not fit the criteria for the study due to confounding diagnosis of sepsis, necrotizing enteroco-

litis and/or PV-IVH occurring after the first week of life. One infant experiencing hyperglycemia (HG) initially, then subsequently developing a PV-IVH at two weeks of life was only included in Group III (hyperglycemia only).

Data were collected from the remaining 57 charts and then subdivided into three groups of preterm infants as follows:

1. Group I: PV-IVH only (N = 6)
2. Group II: PV-IVH with hyperglycemia (N = 33)
3. Group III: Hyperglycemia only (N = 18)

The means, standard deviations and ranges performed for descriptive analysis of the demographic data are presented in Table 1.

Males and females were equally represented in Groups II (PV-IVH/HG) and III (HG). In Group I (PV-IVH), four of the six infants were male, representing 67% of this sample. The small sample size of Group I makes this difference in demographic comparisons difficult to interpret; however, PV-IVH has been reported to occur more frequently in males than females (de Courten & Rabinowicz, 1981; Wigglesworth & Pape, 1980). Birth stress was evidenced by low Apgar scores at one (mean = 3.9) and five minutes (mean = 6.4). The mean one and five minute Apgar scores were higher for

Table 1

Group Comparisons of Demographic Data Means, Standard Deviations and Ranges

Variable	Group I (N) = 6 (PV-IVH)			Group II (N) = 33 (PV-IVH/HG)			Group III (N) = 18 (HG)			Total (N) = 57		
	$\bar{X}$	S.D.	Range	$\bar{X}$	S.D.	Range	$\bar{X}$	S.D.	Range	$\bar{X}$	S.D.	Range
Gestational Age (Weeks)	29	2.4	26-32	31	1.6	27-34	29	2.9	25-34	30	2.2	25-34
Birth Weight (Grams)	1115	277	670-1410	1326	340	790-1950	1191	529	680-2200	1261	405	670-2200
Apgars:												
1 minute	2.2	1.2	1-4	4.7	2.1	1-8	3.1	2.2	1-8	3.9	2.2	1-8
5 minutes	5.5	1.0	4-7	6.7	1.7	3-9	6.2	1.5	2-8	6.4	1.6	2-9
Length of Hospitalization (Days)	34	21.7	8-56	36	22.3	1-93	31	22.9	1-81	34	22.1	1-93

infants in Groups II and III from those in Group I. The average length of hospitalization was 34 days (S.D. 22.1).

More than 80% of the infants in this study sample were born at the University of Utah Medical Center (Table 2). A greater percentage of infants from Group I were transported back to the referring hospital and fewer were sent directly home when compared to infants from Groups II and III. Ten of 57 infants died in this study with a slightly larger percentage of these infants occurring in Group III (22%). The demographic description of this study sample is similar to those reported in other studies (Dykes et al., 1980; Leech & Kohnen, 1974; Shinnar et al., 1982; Wigglesworth & Pape, 1980).

Eighty-nine percent (51/57) of the infants in this study had hyperglycemia (Table 3). Lowering of exogenous glucose input (in 35 of 57 infants) was the primary method of treating the increase in serum glucose values. Five infants in Group III (28%) required the pharmacologic intervention of insulin compared to 9% (3/33) in Group II to combat the hyperglycemia.

Examination of all hyperglycemic subjects revealed that 61% (33/51) of this sample had a PV-IVH. In

Table 2

Type of Admission and Discharge Disposition

Comparison of Groups

Variable	Group I (N) = 6 (PV-IVH) (N)	%	Group II (N) = 33 (PV-IVH/HG) (N)	%	Group III (N) = 18 (HG) (N)	%	Total (N) = 57 (N)	%
Admission:								
Inborn	5	83%	26	79%	15	83%	46	81%
Transported in	1	17%	7	21%	3	17%	11	19%
Discharge:								
Home	2	33%	15	46%	8[a]	44%	25	44%
Basic transport	3	50%	13	39%	5	28%	21	37%
Expired	1	17%	5	15%	4	22%	10	18%

Note. [a]Information not available for one subject.

Table 3

Treatment of Hyperglycemia

Comparison of Groups

Variables	Group II (N) = 33 (PV-IVH/HG) (N)	%	Group III (N) = 18 (HG) (N)	%	Total (N) = 57 (N)	%
Insulin	3	9%	5	28%	8	14%
Low Exogenous Glucose	20	61%	15	83%	35	61%

comparison, 85% (33/39) infants experiencing PV-IVH also demonstrated a hyperglycemic episode.

The overall icidence of PV-IVH in the 57 cases studied was 68% (39/57). This is somewhat greater than the 35-50% reported in the literature (Ahmann et al., 1980; Leech & Kohnen, 1974; Levene & Starte, 1981; Papile et al., 1981; Shinnar et al., 1982).

Documentation of hemorrhage was by echoencephalogram; however, other factors were also noted (Table 4). All PV-IVH episodes were documented at a mean of 4.8 days of life (range 1 to 11 days). Although lumbar punctures were not routinely performed in infants suspected of having a PV-IVH, three infants in Group II (9%) had documentation of blood in the cerebral spinal fluid (CSF). A full fontanelle was observed in only six percent (2/33) of the infants in Group II.

The grading of the severity of PV-IVH followed the criteria described by Papile et al., (1978) as presented in Table 5. The mean age of ventricular-peritoneal shunt placement was 43 days (range = 26-61 days). The subject from Group III (described earlier as developing a PV-IVH after the study period), subsequently required shunt placement and accounts for the fifth infant in this study needing a shunt.

Table 4

Documenting Factors of a PV-IVH Group Comparison

Variable	Group I (N) = 6 $\bar{X}$	S.D.	Range	Group II (N) = 33 $\bar{X}$	S.D.	Range	Total (N) = 57 $\bar{X}$	S.D.	Range
Age of positive echoencephalogram (days)	4.8	2.0	2-8	4.6	1.6	1-8	4.8	1.8	1-11
Age of bloody CSF by lumbar puncture (days)		-		3.0	2.0	1-5	3.2	1.5	1-5
Age of fontanelle change (days)		-		3.5	0.7	3-4	3.0	1.4	1-4

Table 5

Comparison of Severity of PV-IVH and the Need for Shunt Placement

Grade	Group I (N) = 6 (N)	%	Group II (N) = 33 (N)	%	Total (N) = 57 (N)	%
I.	2	33%	14	42%	16	28%
II.	-		4	12%	4	7%
III.	3	50%	8	24%	11	19%
IV.	1	17%	7	21%	8	14%
No IVH	-		-		18	31%
Shunt	1	17%	3	9%	5[a]	9%

Note. [a]One infant from Group III.

Research Question One

Does hyperglycemia occur in relation to the onset of clinical signs of PV-IVH?

Recovering information required to document the onset of PV-IVH from the medical records presented some difficulties. Symptoms associated with subtle or catastrophic deterioration in conjunction with other signs of possible PV-IVH (Lazzara et al., 1980; Volpe, 1981), were inconsistent. Possible explanations for this inconsistency include lack of accurate documentation of clinical events or absence of these specific clinical symptoms (a silent PV-IVH). Therefore, the information gathered from the patient charts was examined only to identify if an association between the variables of PV-IVH and hyperglycemia are related.

To test the association of hyperglycemia in relationship to the occurrence of PV-IVH, the Mantel-Haenszel Chi-square (MH_X^2) analysis was applied. Descriptive statistics on Dextrostix® values and PV-IVH determinations obtained from patient charts were also computed. Graphic illustrations of the range and mean distribution of Dextrostix® values for the three groups of infants are presented in Figures 4-6. Figure 4, depicting the Dextrostix® trends for infants in Group I (PV-IVH) reflects the overall glucose values

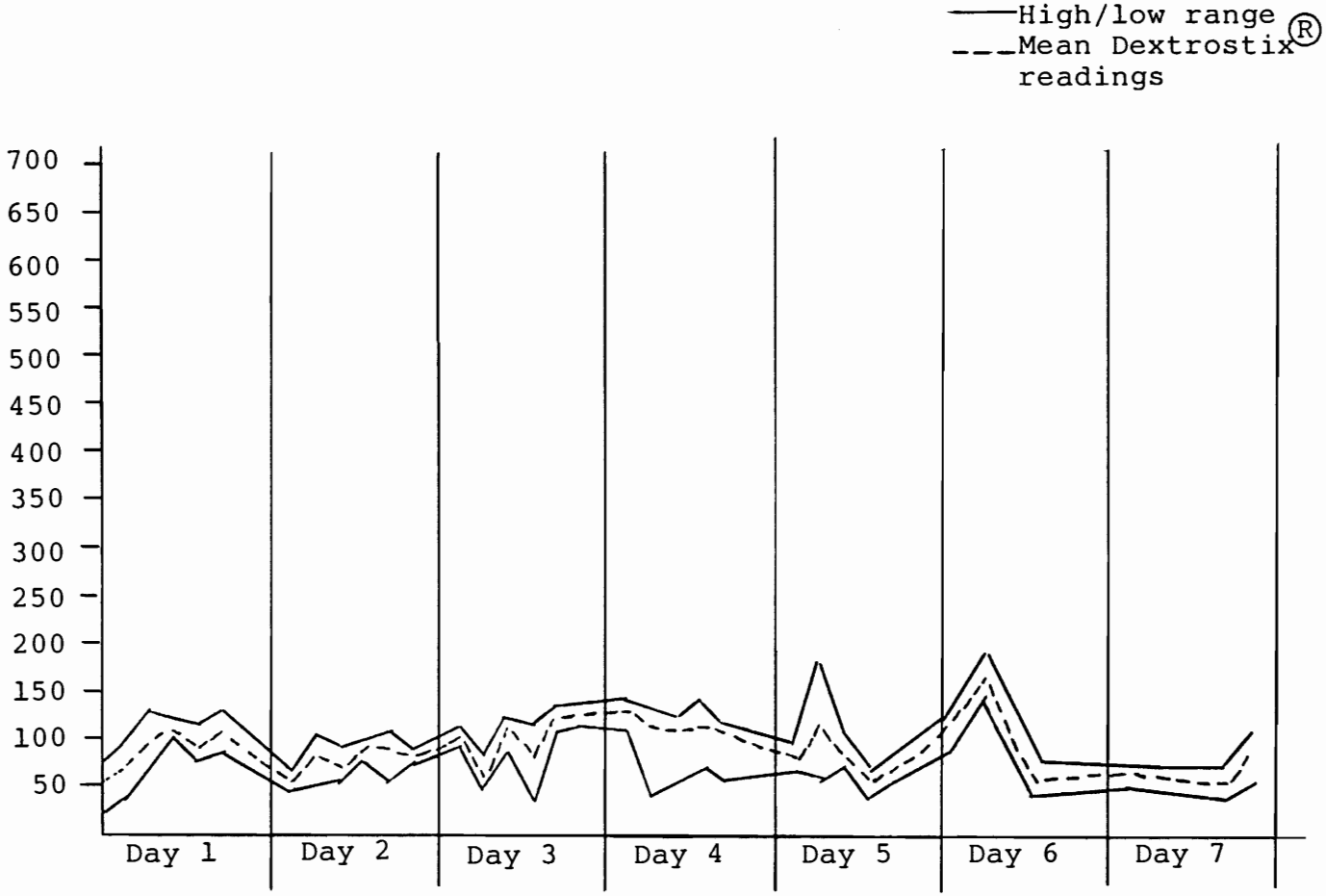

Figure 4. Dextrostix® readings (means and ranges) group I (PV-IVH) (N = 6).

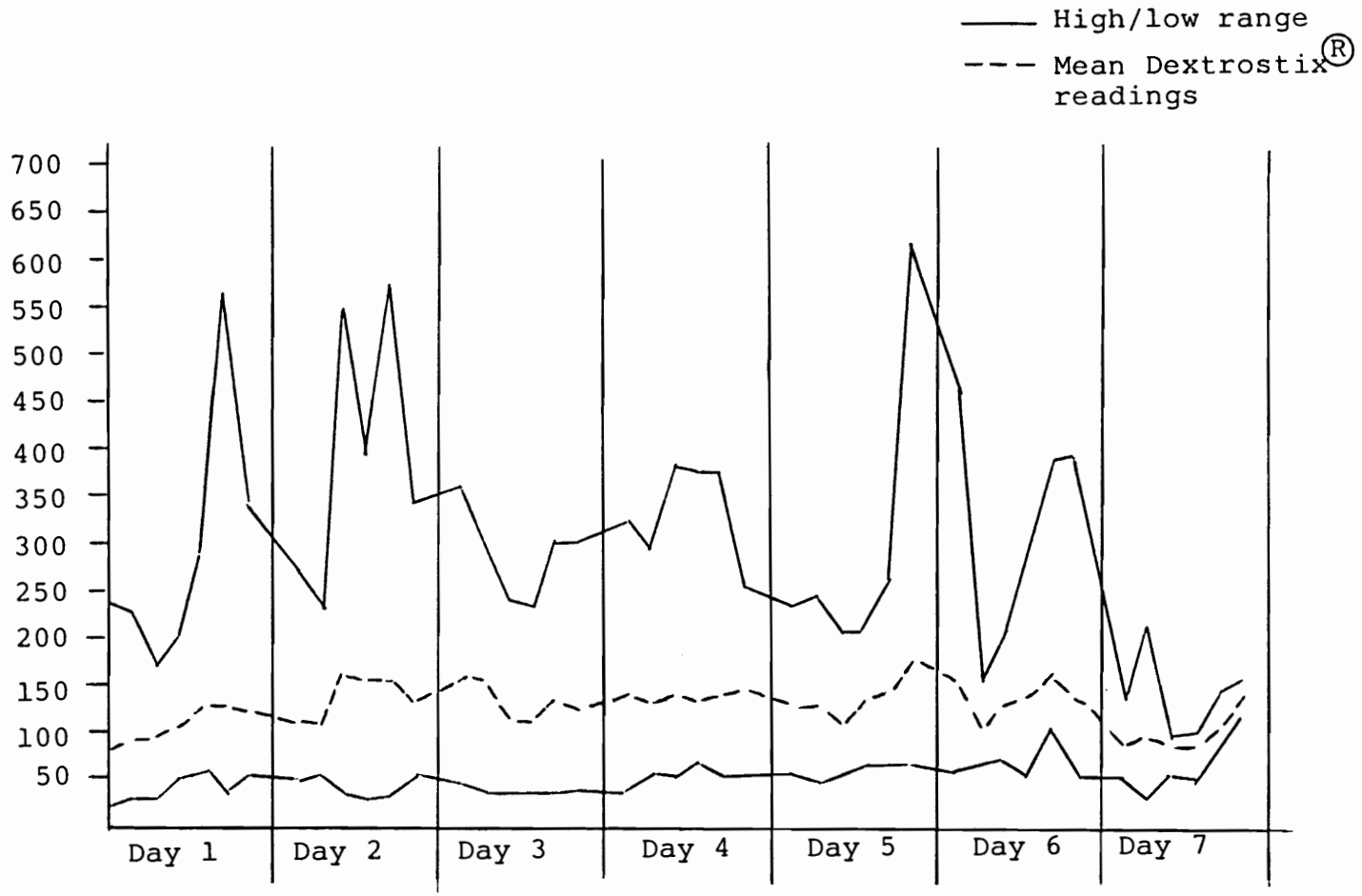

Figure 5. Dextrostix® readings (means and ranges) group II (PV-IVH/HG) (N = 33).

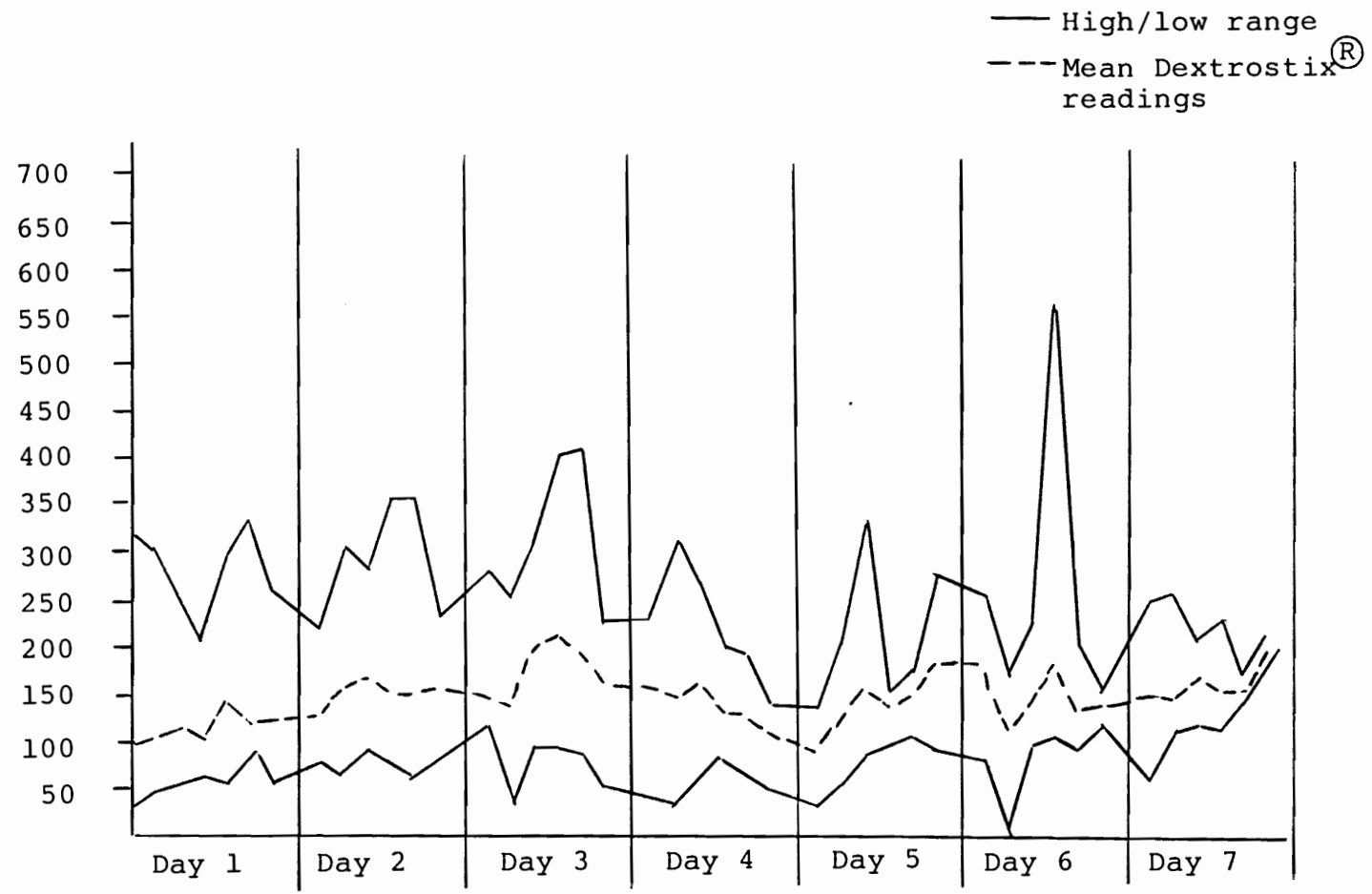

Figure 6. Dextrostix® readings (means and ranges) group III (HG) (N = 18).

within the euglycemic range. Group II (PV-IVH/HG) (Figure 5) had wide ranges of Dextrostix® values, particularly between days two and six. Note the eight hour period on day two with the sudden and dramatic rise of Dextrostix® readings well above the "very severe" glucose value of 250 mg/dl. This sudden rise in glucose level is again seen on days five and six. In Group III (HG) the glucose values consistently trend in the hyperglycemic range (Figure 6). The only sudden rise from baseline noted in this group is on day six.

Stress indicators were evaluated during the time of Dextrostix® recordings. Group comparisons are presented in Table 6. Group I (PV-IVH) infants experienced no cardiorespiratory status deterioration during the first week of life. In Group II (PV-IVH/HG) and III (HG), a rise in the percentage of infants experiencing cardiorespiratory difficulties is noted on day three. Consistently larger percentages of infants in Groups II and III required moderate to maximum ventilatory support. No infant in Group I developed a pneumothorax whereas in Group II pneumothoraces occurred daily until day five. Although all groups experienced hypothermia, Group II (PV-IVH/HG) had a larger percentage of hypothermic subjects.

Table 6

Group Comparisons of Percentages of Stress Experienced

Stress Indicator	Day 1 Group			Day 2 Group			Day 3 Group			Day 4 Group			Day 5 Group			Day 6 Group			Day 7 Group		
	I	II	III	I	II	III	I	II	III	I	II	III	I	II	III	I	II	III	I	II	III
Ventilatory Support																					
Moderate	-	9%	33%	-	15%	17%	17%	27%	28%	-	15%	6%	-	3%	17%	-	-	-	-	3%	-
Maximum	17%	39%	39%	33%	48%	44%	17%	33%	50%	-	18%	39%	-	6%	6%	-	3%	-	-	-	-
Pneumothorax	-	6%	-	-	3%	-	-	3%	-	-	6%	6%	-	-	-	-	-	6%	-	3%	-
Hypothermia	33%	46%	44%	-	27%	17%	17%	24%	17%	17%	15%	6%	-	15%	6%	17%	6%	6%	17%	6%	-
Acidosis	-	18%	11%	17%	27%	22%	-	21%	28%	-	6%	22%	-	3%	6%	-	3%	-	-	-	-
Cardiopulmonary Deterioration	-	9%	17%	-	15%	11%	-	27%	33%	-	9%	17%	-	3%	6%	-	3%	-	-	3%	-

Acidosis was encountered in larger percentage in Groups II and III primarily on days one through three.

In summary, Group II (PV-IVH/HG) and III (HG) infants had larger percentages of infants experiencing stressful events, notably during the first three to four days of life. Dextrostix® values of these same groups show the widest ranges of values on days one through four. Sudden rises of Dextrostix® values from baseline were seen primarily on days two through five.

The Mantel-Haenszel Chi-square (MH_X^2) analysis demonstrated a significant correlation between the occurrence of hyperglycemia and PV-IVH on all seven days of the study period (Table 7).

The cumulative data for the sample studied demonstrated a risk ratio of these two variables occurring together of 12.10 ($p < .000001$).

The methodology of this study does not allow the establishment of a temporal relationship between the hyperglycemia and PV-IVH. However, the significant risk of these two factors occurring together can be addressed. Animal studies have shown an increased survival time following anoxic stress with infusion of exogenous glucose (Holowack-Thurston, Hauhard & Jones, 1974). The fall in brain glucose levels in

Table 7

Mantel-Haenszel Chi-square Analysis

of Hyperglycemia and PV-IVH

Day	Risk Ratio	P Value
1	12.83	.000001
2	7.70	.00001
3	9.10	.000001
4	9.85	.000001
5	18.57	.000001
6	13.57	.000001
7	9.90	.00024

anoxia was suggested to reflect an increase in cerebral anaerobic glycolysis which exceeded the increase in glucose transfer. However, the lower cerebral glucose values did not correspondingly result in lower plasma values. Pancreatic output of insulin is also found to be diminished with most forms of shock and circulatory failure (Baum & Porte, 1980; Cerchio et al., 1973; Shamoon et al., 1981). The stress (hypoxia, circulatory collapse, shock) occurring with PV-IVH could:

1. lower perfusion to the pancreas resulting in diminished portal and peripheral insulin levels and/or

2. result in endogenous catecholamine release inhibiting the pancreatic beta-cell function in producing insulin (Cerchio et al., 1973).

The hypoinsulinemia leads to elevated serum glucose levels which can then be diverted to noninsulin dependent tissues (i.e., central nervous system) to meet the increased energy requirements experienced during acute shock states (Baum & Porte, 1980).

This concept is further supported by studies demonstrating that the relatively low cerebral blood flow of the germinal matrix area (Ment et al., 1981; Pasternak, Groothus, Fischer & Fischer, 1982), selectively increases in the presence of PV-IVH without the corresponding increase in cerebral metabolic rate. Under these conditions (increased

cerebral blood flow without increased cerebral metabolic rate), animal studies demonstrate widespread alterations in local cerebral glucose utilization. In the adult rat, glucose uptake of the periventricular white matter increased while other brain regions decreased (Pulsinelli & Duffy, 1979). The resultant uniformity of cerebral glucose uptake differs from the normal heterogeneity of cerebral glucose utilization, thus providing a small amount of glucose substrate uniformly throughout the brain during a stressful event.

The use of positive emission tomography has demonstrated not only the reduced cerebral blood flow to the area of hemorrhage intracerebral involvement, but also a marked reduction in blood flow throughout the affected hemisphere (Volpe, Herscovitch, Perlman & Raichle, 1983). With the sudden reduction in blood flow, one could surmise that cerebral glucose utilization would also decline and result in an elevation in serum glucose levels.

Further analysis of the data (MH_X2) included investigation of the correlation of PV-IVH with the various stress indicators listed in Table 7. Requirement of maximum or moderate ventilatory support ($p < .000001$) and/or the occurrence of a pneumothorax ($p < .00018$) were the only factors significantly cor-

related with the occurrence of PV-IVH (Table 8).

A close temporal relationship of PV-IVH and pneumothorax has been reported (Dykes et al., 1980; Hill, Perlman & Volpe, 1982). The increased intrathoracic pressure experienced with pneumothorax leads to the cardiovascular hemodynamic changes which increase the flow to the anterior cerebral artery. This can potentiate and/or cause a PV-IVH in a predisposed infant.

Reports of respiratory distress and the subsequent need for mechanical ventilatory assistance is significantly related to the occurrence of PV-IVH (Cooke, 1981; Levene et al., 1982). Other risk factors such as hypercarbia and acidosis seemed to be related to the respiratory distress experienced by preterm infants. The increase in $PaCO_2$ and the decrease in the blood pH has been postulated to result in cerebral vasodilatation which is an etiologic factor in PV-IVH (Levene et al., 1982; Wigglesworth, Davies, Keith & Slade, 1977). In contrast, Bucciarelli and Eitzman (1979), demonstrated in goats the linear relationship of cerebral blood flow to hydrogen ion content being independent of $PaCO_2$ values. Papile and colleagues (1978) reported an in vivo study in which these perinatal factors as well as the need for respiratory

Table 8

Mantel-Haenszel Chi-square Analysis of

PV-IVH and Stress Indicators (N) = 57

Stress Indicator	Risk Ratio	P-Value
Ventilatory Support	13.928	.000001
Pneumothorax	15.395	.00018
Hypothermia	1.099	.884
Acidosis	.804	.932
Cardiorespiratory Deterioration	.517	.405

assistance was not related to the development of an intraventricular hemorrhage. In the present study, acidosis, hypothermia, and cardiorespiratory status deterioration did not demonstrate a significant risk for the development of a PV-IVH in this sample. The possible difficulty in identifying clinical features of a PV-IVH is acknowledged due to the wide variations of presentation. Only those infants demonstrating a catastrophic deterioration at the time of the PV-IVH were readily identified. Other cases experiencing more subtle deterioration or those clinically not evident may have been unidentifiable by the chart review.

The MH_X^2 analysis was also employed to examine the correlation between the five stress indicators with the occurrence of hyperglycemia (Table 9). Cardiorespiratory status deterioration was the only variable significantly correlated ($p < .05$) with hyperglycemia.

The statistical significance of cardiopulmonary deterioration with the occurrence of hyperglycemia has been reported by others, suggesting an adrenergic mechanism responding to the stress factors comprising this category (Baum & Porte, 1980). The weakly correlated stress indicator of ventilatory support

Table 9

Mantel-Haenszel Chi-square Analysis of Hyperglycemia and the Stress Indicators (N = 57)

Stress Indicator	Risk Ratio	P-Value
Ventilatory Support	6.500	.084
Pneumothorax	2.540	.674
Hypothermia	2.923	.437
Acidosis	5.625	.216
Cardiorespiratory Deterioration	14.592	.045

(p = 0.084) to hyperglycemia may reflect the interrelatedness of respiratory distress, hypoxemia, hypercarbia, and acidosis to the overall category of cardiopulmonary deterioration (Bucciarelli & Eitzman, 1979; Levene et al., 1982; Wigglesworth et al., 1977). The stress responsible for the glucose intolerance may even be a result of massive intracranial hemorrhage (Cepeda, Heilbronner & Poland, 1978).

The mortality rate among hyperglycemic infants has been reported to be more closely associated with the stress rather than the hyperglycemia involved (Lilien et al., 1979). Data from this study support this postulation. Group III (HG) had the largest percentage (22%) of the infants that died (Table 2). The mortality rate from groups I and II was 17% and 15%, respectively. Group II's infants also experienced a greater percentage of stressful events (Table 7).

While exogenous glucose infusions have been reported to be higher in infants with glucose intolerance in the presence of PV-IVH (Cepeda et al., 1978), glucose infusions did not vary significantly among the three groups of infants in this study (Table 10).

Research Question Two

Is the degree of glucose intolerance

Table 10

Mean Glucose Infusion Values

Group Comparisons

Group	(N)	Glucose Infusions
I	6	7.3 mg/kg/minute
II	33	7.1 mg/kg/minute
III	18	7.4 mg/kg/minute

reflective of the grade of the PV-IVH?

Descriptive statistics, the Spearman rho correlation coefficient and the Mann-Whitney U tests were used to analyze the association of the degree of glucose intolerance reflecting the grade of PV-IVH. The Dextrostix® readings and the echoencephalogram interpretations, used to grade the PV-IVH (Table 5), were obtained from the medical records.

Determination of Spearman's rho showed no significant correlation between the degree of hyperglycemia and the grade of PV-IVH. However, further analysis of the data by the Mann-Whitney U test revealed a significant relationship between the degree of hyperglycemia and just the occurrence of a PV-IVH ($U = 161.5$; $p < 0.132$).

The increases in serum osmolality exceeding 25-40 mOms/liter of water associated with intracranial hemorrhage (Finberg, 1967) would require a serum glucose value of greater than 250-400 mg/100 ml of blood. Others have reported that an increased incidence of PV-IVH indeed, does occur when blood glucose values exceed the 400 mg/100 ml of blood (Zarif et al., 1976). The findings of this study sample are consistent with the above findings in that the degree of hyperglycemia is significantly

associated with the occurrence of PV-IVH. However, it is not predictive of the severity of PV-IVH.

In attempting to discuss the etiologic components that determine the extent of a PV-IVH, examination of multiple factors are necessary. The maturity of the infant influences the intravascular and extravascular forces, cerebral metabolic rate, capillary integrity, the supporting capacity of the basement membrane and other pathogenetic risk factors of PV-IVH (Dykes et al., 1980; Gruenwald, 1951; Hambleton & Wigglesworth, 1976; Ment et al., 1981; Pasternak et al., 1982; Volpe, 1981; Wigglesworth & Pape, 1980).

Various endogenous and autoregulatory responses to the stress experienced by a small pretern infant influence the cerebral blood flow (Bada et al., 1982; Bucciarelli & Eitzman, 1979; Cooke et al., 1979; de Courten & Rabinowicz, 1981; Hill et al., 1982; Lou et al., 1977; Ment et al., 1981; Wigglesworth et al., 1977). Other physiologic maturity factors such as capillary integrity (Volpe, 1981) and transmural pressure gradients (Conner et al., 1983; Coulter, 1980; Goldstein, 1979; Welch, 1980) then determine the response to the increase in cerebral blood flow. Clinical factors such as hypoxic-ischemic injury to the immature cerebral structures further complicate

the ability of fragile cerebral vessels and gelatinous vascular supporting structures to accomodate a sudden increase in cerebral blood flow (Fujimura et al., 1979; Volpe, 1981). Neonatal germinal matrix hemorrhage has also been reported to be a progressive lesion (Conner et al., 1983; Donn & Stuck, 1981), perhaps due to the reported increase in fibrinolytic activity of the periventricular region of the preterm infant (Volpe, 1981).

Variables affecting the occurrence of hyperglycemia are also multifactorial in nature. Neuroendocrine response (Fisher, 1975; Pollak et al., 1978; Salle & Ruitton-Uglienco, 1976; Sherwood & Chance, 1977), peripheral tissue sensitivity to insulin (Goldman & Hirata, 1980; Pollak et al., 1978; Zarif et al., 1976), and/or stress (Baum & Porte, 1980; Cerchio et al., 1973; Zarif et al., 1976) have all been investigated in association with hyperglycemia in the preterm infant.

The multitude of components involved in determining the extent of a PV-IVH and/or hyperglycemia is unique to each individual and may or may not be interrelated. These reports would therefore lend support to the lack of correlation in this study sample between the degree of hyperglycemia and the

subsequent grade of the PV-IVH.

Research Question Three

> Is the degree of hyperglycemia, regardless of the grade of PV-IVH, related to the development of posthemorrhagic hydrocephalus (PHH)?

The relationship between the degree of hyperglycemia and the development of posthemorrhagic hydrocephalus (PHH) was analyzed by descriptive statistics and the Mann-Whitney U test. Information collected to determine the surgical placement of a ventriculo-peritoneal shunt (used to define PHH in this study) (Table 5) was obtained from the patient's medical records. The Mann-Whitney U analysis showed no significant relationship between the severity of hyperglycemia and the subsequent necessity for a shunt (Table 11).

The incidence of PHH in the literature was varied. This discrepancy in the reported incidence is most likely due to the technological advances made in ultrasonography which has facilitated the diagnosis and follow-up on ventricular dilatation, as well as the development of hydrocephalus. Current studies report a 20-35% incidence of PHH as detected by echoencephalogram (Ahmann et al., 1980; Levene & Starte, 1981; Williamson et al., 1982).

Table 11

Mann-Whitney U Results for the Relationship of Hyperglycemia and Hydrocephalus (N = 5)

Day	U-Value	P-Value
1	120.5	.8454
2	101.5	.5420
3	97.5	.5050
4	90.5	.6810
5	45.5	.9545
6	30.5	.6885
7	14.0	.2211

Studies have repeatedly demonstrated that serial occipitalfrontal circumferences are poor determinants of early PHH (Ahmann et al., 1980; Bridgers & Ment, 1981; Papile et al., 1980). In careful ultrasonographic follow-up of posthemorrhagic ventricular dilatation, most cases are found to spontaneously resolve and not require surgical shunting procedures (Ahmann et al., 1980; Levene & Starte, 1981). These reports served as the basis for defining PHH in this study sample as infants requiring a ventriculo-peritoneal shunt.

PV-IVH has been described as being a progressive lesion (Connor et al., 1983; Donn & Stuck, 1981) and a significant relationship seemed to exist between the quantification of hemorrhage to the development of PHH. Therefore, one may speculate that the initial protein content of CSF may be more predictive of the subsequent need for a shunt, rather than the degree of hyperglycemia. As described in the previous section (research question two), a multitude of factors are involved in the pathogenetic mechanisms of hyperglycemia as well as PV-IVH. Thus, information gathered from this study sample could not demonstrate a relationship between severity of hyperglycemia and subsequent need for a shunt.

CHAPTER V

SUMMARY, CONCLUSIONS AND RECOMMENDATIONS

Summary

The purpose of this study was to determine the relationship between the onset of PV-IVH and the occurrence of hyperglycemia. However, recovering information from the charts required to pinpoint the onset of the PV-IVH, presented major difficulties to this study. The information gathered from the patient's charts was, therefore, examined only to identify if an association between the variables of PV-IVH and hyperglycemia were related.

The General Systems Theory was the basis for this study's conceptual framework. When the mutually interacting systems within the human body experience a stress, the preservation of an intact system may potentially be facilitated by nurses, who identify the disturbance. The proposed mechanism of stress, hyperglycemia and/or PV-IVH was presented.

The review of literature demonstrated the high

incidence of PV-IVH in the preterm infant. Several studies identifying risk factors associated with PV-IVH were presented. Various proposals on etiologic factors of neonatal hyperglycemia were reviewed. Studies potentially linking hyperglycemia with PV-IVH were also available for examination. If a relationship between glucose intolerance and PV-IVH could be demonstrated, hyperglycemia may in the future give warning to a new or impending PV-IVH. This would facilitate the prompt initiation of therapy to provide optimal survival of these infants.

The study sample consisted of 57 preterm infants from the University of Utah Medical Center's NICU who were diagnosed with hyperglycemia, PV-IVH or hyperglycemia and PV-IVH. A retrospective review of their medical records was conducted for this investigation.

The first research question was modified to determine if an association between the variables of hyperglycemia and PV-IVH are related. Identification of the onset of PV-IVH was not possible in this study. The determination of risk of the stress indicators occurring with the variables of hyperglycemia and PV-IVH was conducted. Ventilatory support and the development of a pneumothorax were significantly

correlated with the occurrence of a PV-IVH. Cardiopulmonary deterioration was statistically significant and ventilatory support only weakly significant in relationship to the occurrence of hyperglycemia. Overall, the data analysis demonstrated a significant risk for the development of hyperglycemia in relationship to PV-IVH.

The second research question examined the relationship between the degree of glucose intolerance to the grade of PV-IVH experienced. No significant correlation was demonstrated between the degree of glucose intolerance to the subsequent grade of PV-IVH. The occurrence of a PV-IVH however, was statistically significant in association with a hyperglycemic episode occurring in the clinical course of this preterm study sample.

Research question three attempted to describe a relationship between the degree of glucose intolerance and the subsequent development of PHH (defined as needing a ventriculo-peritoneal shunt). There was no significant relationship between the severity of hyperglycemia and the subsequent need for a shunt.

Conclusions

The findings from this study suggest that a relationship may exist between hyperglycemia and

PV-IVH. The clinical value of glucose determinations may serve to identify a new or impending PV-IVH. The severity of hyperglycemia cannot predict the extent of a PV-IVH or the subsequent need for a ventriculo-peritoneal shunt. A controlled prospective study with a larger study sample may provide information to validate this relationship. If the relationship between hyperglycemia and PV-IVH can be demonstrated, nurses may be able to utilize the glucose value (or Dextrostix®) as a tool to identify infants at risk for PV-IVH or intervene to prevent complications of a newly occurred PV-IVH. The overall contribution of this study exists in its capacity to expand the knowledge base of this serious neonatal complication.

Recommendations

Recommendations for further research include:

1. Conduct a prospective study with a large sample size, controlling for confounding variables and providing a consistent measurement of serum glucose values and echoencephalographic imaging.

2. A continuous, noninvasive method of measuring cerebral blood flow could be utilized to examine this factor in relationship to serum glucose levels and the occurrence of PV-IVH.

3. A continuous method of measuring serum glucose values would facilitate the identification of blood glucose fluctuations in response to a variety of clinical stress factors associated with a preterm infant.

4. Continuous measurement of arterial and/or peripheral blood pressure values correlated with cerebral blood flow and/or serum glucose values would further clarify the relationship among these variables.

5. Measurement of other substrates reflective of a stress response such as urine catecholamine levels to determine if hyperglycemia is a response to stress.

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